CASE 33310-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF
Atadja, Peter Wisdom et al.
INTERNATIONAL APPLICATION NO: PCT/EP2004/008848
FILED: August 06, 2004
U.S. APPLICATION NO: 10/567897
35 USC §371 DATE: September 22, 2006
FOR: Combinations Comprising Staurosporines

Art Unit: 1611
Examiner: Rae, Charlesworth E

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

NOTICE OF APPEAL

Sir:

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the Office Action dated January 5, 2009 finally rejecting claims 1-14.

☒ Please charge Deposit Account No. 19-0134 in the name of Novartis in the amount of $540 for payment of the appeal fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

☐ The appeal fee was paid in a previous appeal herein. The examiner re-opened prosecution prior to any decision by the Board of Patent Appeals and Interferences. No fee is now due.

☒ Enclosed is a Petition for Extension of Time.

Respectfully submitted,

George Dohmann
Attorney for Applicant
Reg. No. 33,593

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-7824

Date: 5/29/09

Response Under 37 CFR §1.116
Expedited Procedure
Examining Group 1611

CASE 33310-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
ATADJA ET AL.
APPLICATION NO: 10/567,897
FILED: SEPTEMBER 22, 2006
FOR: COMBINATIONS COMPRISING STAUROSPORINES

Art Unit: 1611
Examiner: Rae, Charlesworth E.

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER FINAL REJECTION

Sir:

In response to the Office action dated January 5, 2009, response due April 5, 2009, here extended two months by simulaneously filed Petition for Extension of Time to be due on June 5, 2009, kiindly enter the following response.

Amendments to the Claims begin on page 2.

Remarks/Arguments begin on page 11.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions:

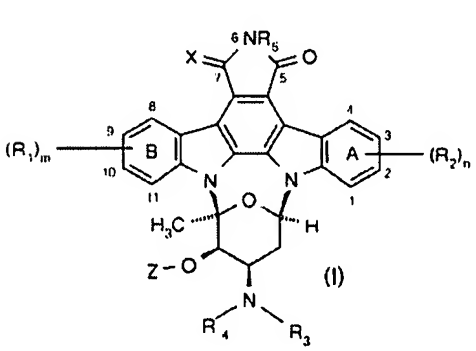
Listing of Claims:

1. (currently amended) A method of treating myelodysplastic syndromes, lymphomas and leukemias , and solid tumors comprising cells that express constitutively active mutant FLT-3 in a mammal which comprises treating the mammal in need of such treatment simultaneously, concurrently, separately or sequentially with pharmaceutically effective amounts of (a) a FLT-3 inhibitor, or a pharmaceutically acceptable salt ~~or a prodrug~~ thereof, and (b) a histone deacetylase inhibitor (HDAI), or a pharmaceutically acceptable salt or a prodrug thereof.

2. (original) The method according to claim 1 for treating acute myeloid leukemia (AML) .

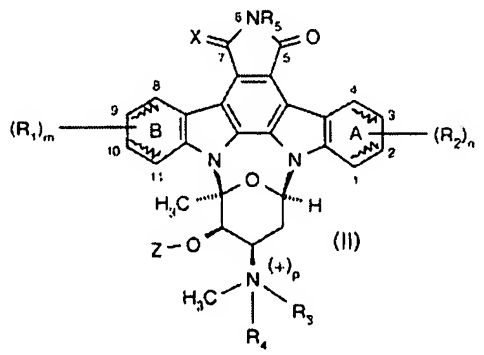
3. (cancelled)

4. (currently amended) The method according to claim 1, wherein the FLT-3 inhibitor is a staurosporine derivative ~~is~~ selected from the compounds of formula,

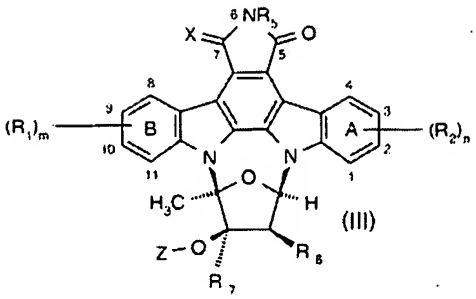


(I)

or

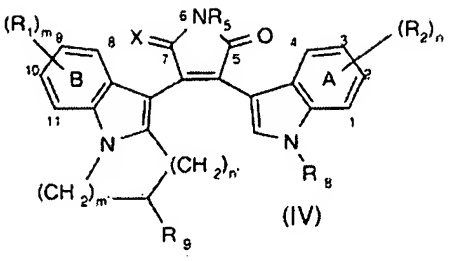


(II)



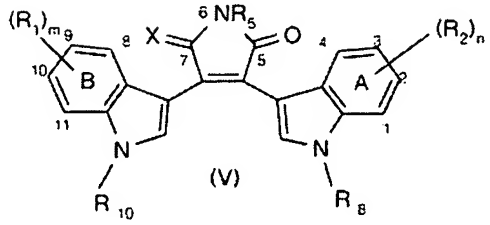
(III)

or



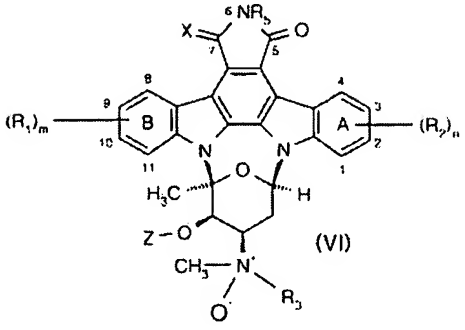
(IV)

or



(V)

or



(VI)

or

wherein R_1 and R_2, are, independently of one another, unsubstituted or substituted alkyl, hydrogen, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

n and m are, independently of one another, a number from ~~and including~~ 0 to ~~and including~~ 4;

n' and m' are, independently of one another, a number from ~~and including~~ 1 to ~~and including~~ 4;

R_3, R_4, R_8 and R_{10} are, independently of one another, hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, an acyl with up to 30 carbon atoms, wherein R_4 may also be absent;

or R_3 is acyl with up to 30 carbon atoms and R_4 not an acyl;

p is 0 if R_4 is absent, or is 1 if R_3 and R_4 are both present and in each case are one of the aforementioned radicals;

R_5 is hydrogen, an aliphatic, carbocyclic, or carbocyclic-aliphatic radical with up to 29 carbon atoms in each case, or a heterocyclic or heterocyclic-aliphatic radical with up to 20 carbon atoms in each case, and in each case up to 9 heteroatoms, or acyl with up to 30 carbon atoms;

R_7, R_8 and R_9 are acyl or –(lower alkyl) –acyl, unsubstituted or substituted alkyl, hydrogen, halogen, hydroxy, etherified or esterified hydroxy, amino, mono- or disubstituted amino, cyano, nitro, mercapto, substituted mercapto, carboxy,carbonyl, carbonyldioxy, esterified carboxy, carbamoyl, N-mono- or N,N-di-substituted carbamoyl, sulfo, substituted sulfonyl, aminosulfonyl or N-mono- or N,N-di-substituted aminosulfonyl;

X stands for 2 hydrogen atoms; for 1 hydrogen atom and hydroxy; for O; or for hydrogen and lower alkoxy;

Z stands for hydrogen or lower alkyl;

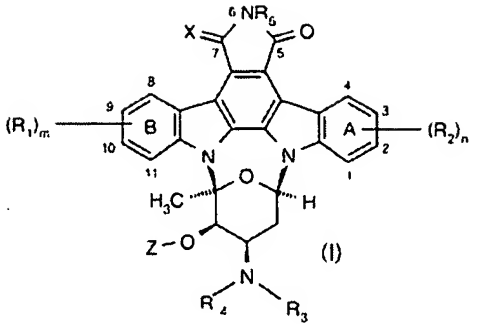
and either the two bonds characterised by wavy lines are absent in ring A and replaced by 4 hydrogen atoms, and the two wavy lines in ring B each, together with the respective parallel bond, signify a double bond;

or the two bonds characterised by wavy lines are absent in ring B and replaced by a total of 4 hydrogen atoms, and the two wavy lines in ring A each, together with the respective parallel bond, signify a double bond;

or both in ring A and in ring B all of the 4 wavy bonds are absent and are replaced by a total of 8 hydrogen atoms;

or a salt thereof, if at least one salt-forming group is present.

5. (currently amended) The method according to claim 4 ~~3~~, wherein the staurosporine derivative is a staurosporin derivative of formula I,



(I)

wherein

m and n are each 0;

R_3 and R_4 are independently of each other

hydrogen,

lower alkyl unsubstituted or mono- or disubstituted, especially monosubstituted, by radicals selected independently of one another from carboxy; lower alkoxycarbonyl; and cyano;

or

R_4 is hydrogen or -CH_3, and

R_3 is acyl of the subformula R^o-CO, wherein R^o is lower alkyl; amino-lower alkyl, wherein the amino group is present in unprotected form or is protected by lower alkoxycarbonyl; tetrahydropyranyloxy-lower alkyl; phenyl; imidazolyl-lower alkoxyphenyl; carboxyphenyl; lower alkoxycarbonylphenyl; halogen-lower alkylphenyl; imidazol-1-ylphenyl; pyrrolidino-lower alkylphenyl; piperazino-lower alkylphenyl; (4-lower alkylpiperazinomethyl)phenyl; morpholino-lower alkylphenyl; piperazinocarbonylphenyl; or (4-lower alkylpiperazino)phenyl;

or is acyl of the subformula R^o-O-CO-, wherein R^o is lower alkyl;

or is acyl of the subformula R^oHN-C(=W)-, wherein W is oxygen and R^o has the following meanings: morpholino-lower alkyl, phenyl, lower alkoxyphenyl, carboxyphenyl, or lower alkoxycarbonylphenyl;

or R_3 is lower alkylphenylsulfonyl, typically 4-toluenesulfonyl;

R_5 is hydrogen or lower alkyl,

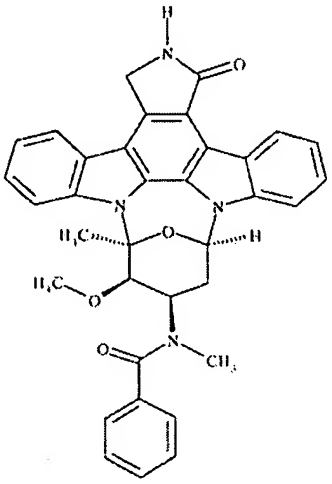
X stands for 2 hydrogen atoms or for O;

Z is methyl or hydrogen;

or a salt thereof, if at least one salt-forming group is present.

6. (currently amended) The method according to claim 4 3, wherein the staurosporine derivative is *N*-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-

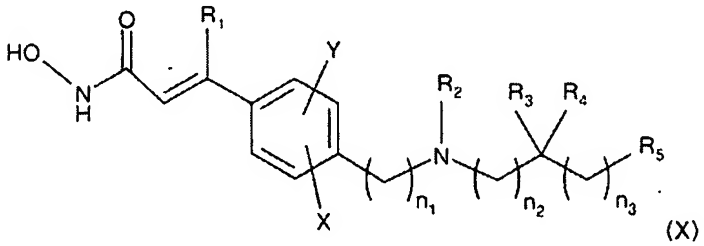
epoxy-1*H*,9*H*-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-*N*-methylbenzamide of the formula (VII):



(VII)

or a salt thereof.

7. (original) The method according to claim 1, wherein the HDAI compound is a histone deacetylase inhibitor of formula (X)



(X)

wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl;

R_2 is selected from H, C_1-C_{10} alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, C_4 – C_9 heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_8$, $-(CH_2)_nOC(O)R_6$, amino acyl, HON-C(O)-CH=C(R_1)-aryl-alkyl- and $-(CH_2)_nR_7$;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound represent C=O, C=S, or C=NR_8, or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound can form a C_4 – C_9 heterocycloalkyl, a heteroaryl, a

polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, acyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, and mixed aryl and non-aryl polyheterocycle;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0 – 6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, NO_2, $C(O)R_1$, OR_9, SR_9, CN, and $NR_{10}R_{11}$;

R_6 is selected from H, C_1-C_6 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR_{12}, and $NR_{13}R_{14}$;

R_7 is selected from OR_{15}, SR_{15}, $S(O)R_{16}$, SO_2R_{17}, $NR_{13}R_{14}$, and $NR_{12}SO_2R_6$;

R_8 is selected from H, OR_{15}, $NR_{13}R_{14}$, C_1-C_6 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R_9 is selected from C_1 – C_4 alkyl and C(O)-alkyl;

R_{10} and R_{11} are the same or different and independently selected from H, C_1-C_4 alkyl, and -C(O)-alkyl;

R_{12} is selected from H, C_1-C_6 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, C_4 – C_9 heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl, and heteroarylalkyl;

R_{13} and R_{14} are the same or different and independently selected from H, C_1-C_6 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, amino acyl, or R_{13} and R_{14} together with the nitrogen to which they are bound are C_4 – C_9 heterocycloalkyl, heteroaryl, polyheteroaryl, non-aromatic polyheterocycle or mixed aryl and non-aryl polyheterocycle;

R_{15} is selected from H, C_1-C_6 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{16} is selected from C_1-C_6 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, aryl, heteroaryl, polyheteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_mZR_{12}$;

R_{17} is selected from C_1-C_6 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, aryl, aromatic polycycle, heteroaryl, arylalkyl, heteroarylalkyl, polyheteroaryl and $NR_{13}R_{14}$;

m is an integer selected from 0 to 6; and

Z is selected from O, NR_{13}, S and S(O);

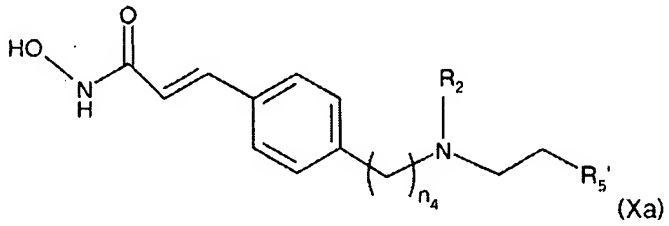
or a pharmaceutically acceptable salt thereof.

8. (original) The method according to claim 7, wherein each of R_1, X, Y, R_3, and R_4 is H.

9. (original) The method according to claim 8, wherein one of n_2 and n_3 is zero and the other is 1.

10. (original) The method according to claim 9, wherein one of n_2 and n_3 is zero and the other is 1.

11. (original) The method according to claim 1, wherein the histone deacetylase inhibitor is a compound of the formula (Xa)



(Xa)

wherein

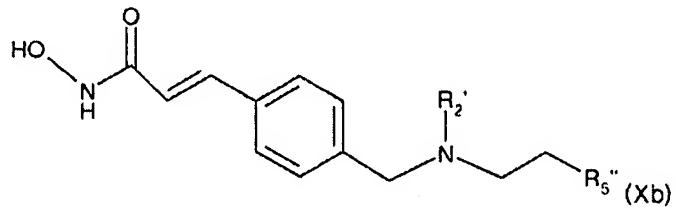
n_4 is 0-3,

R_2 is selected from H, C_1-C_8 alkyl, C_4 – C_9 cycloalkyl, C_4 – C_9 heterocycloalkyl, alkylcycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, amino acyl and $-(CH_2)_nR_7$;

R_5' is heteroaryl, heteroarylalkyl, an aromatic polycycle, a non-aromatic polycycle, a mixed aryl and non-aryl polycycle, polyheteroaryl, or a mixed aryl and non-aryl polyheterocycle

or a pharmaceutically acceptable salt thereof.

12. (original) The method according to claim 1, wherein the histone deacetylase inhibitor is a compound of the formula (Xb):



(Xb)

wherein

R_2' is selected from H, C_1-C_6 alkyl, C_4-C_6 cycloalkyl, alkylcycloalkyl, and $(CH_2)_{2\text{-}4}OR_{21}$ where R_{21} is H, methyl, ethyl, propyl, or isopropyl, and

R_5" is unsubstituted or substituted 1*H*-indol-3-yl, benzofuran-3-yl or quinolin-3-yl

or a pharmaceutically acceptable salt thereof.